# Vitamin E supplementation in pregnancy (Review)

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[Intervention Review]

# Vitamin E supplementation in pregnancy

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## ABSTRACT

### Background

Vitamin E supplementation may help reduce the risk of pregnancy complications involving oxidative stress, such as pre-eclampsia. There is a need to evaluate the efficacy and safety of vitamin E supplementation in pregnancy.

### Objectives

To assess the effects of vitamin E supplementation, alone or in combination with other separate supplements, on pregnancy outcomes, adverse events, side-effects and use of health services.

### Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (23 June 2004), the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 2, 2004), MEDLINE (1966 to May 2004), Current Contents (1998 to May 2004) and EMBASE (1980 to May 2004). We updated the search of the Cochrane Pregnancy and Childbirth Group's Trials Register on 7 May 2010 and added the results to the awaiting classification section.

### Selection criteria

All randomised or quasi-randomised controlled trials evaluating vitamin E supplementation in pregnant women. We excluded interventions using a multivitamin supplement that contained vitamin E.

### Data collection and analysis

Two authors independently assessed trials for inclusion, extracted data and assessed trial quality.

### Main results

Four trials, involving 566 women either at high risk of pre-eclampsia or with established pre-eclampsia, were eligible for this review. All trials assessed vitamin E in combination with other supplements and two trials were published in abstract form only. No difference was found between women supplemented with vitamin E in combination with other supplements during pregnancy compared with placebo for the risk of stillbirth (relative risk (RR) was 0.77, 95% confidence intervals (CI) 0.35 to 1.71, two trials, 339 women), neonatal death (RR 5.00, 95% CI 0.64 to 39.06, one trial, 40 women), perinatal death (RR 1.29, 95% CI 0.67 to 2.48, one trial, 56 women), preterm birth (RR 1.29, 95% CI 0.78 to 2.15, two trials, 383 women), intrauterine growth restriction (RR 0.72, 95% CI 0.49 to 1.04, two trials, 383 women) or birthweight (weighted mean difference -139.00 g, 95% CI -517.68 to 239.68, one trial,

100 women), using fixed-effect models. Substantial heterogeneity was found for pre-eclampsia. Women supplemented with vitamin E in combination with other supplements compared with placebo were at decreased risk of developing clinical pre-eclampsia (RR 0.44, 95% CI 0.27 to 0.71, three trials, 510 women) using fixed-effect models; however, this difference could not be demonstrated when using random-effects models (RR 0.44, 95% CI 0.16 to 1.22, three trials, 510 women). There were no differences between women supplemented with vitamin E compared with placebo for any of the secondary outcomes.

**Authors' conclusions**

The data are too few to say if vitamin E supplementation either alone or in combination with other supplements is beneficial during pregnancy.

[Note: The 24 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

## PLAIN LANGUAGE SUMMARY

**Vitamin E supplementation in pregnancy**

Not enough evidence to determine if giving women vitamin E during pregnancy helps prevent their babies dying, being born small or too soon.

For pregnant women, insufficient dietary vitamin E (found in vegetable oils, nuts, cereals and some leafy green vegetables) may lead to complications like pre-eclampsia and the baby being born small. The review of trials found no studies on vitamin E supplementation alone, but studies included vitamin C, and additional supplements or drugs. There was not enough evidence to say if vitamin E in combination with other supplements during pregnancy improved outcomes for women and babies.

## BACKGROUND

Vitamin E is the generic name given to eight lipid soluble and plant-derived compounds, four are referred to as tocopherols (alpha, beta, gamma, delta) and four are known as tocotrienols (alpha, beta, gamma, delta) (Roberts 1990). Natural source alpha-tocopherol is the most biologically active form of vitamin E, and consequently vitamin E activity is expressed in terms of alpha-tocopherol equivalents (mg alpha-TE). In foods, tocopherol is found highest in wheatgerm oil and other vegetable oils, nuts, some cereals and some leafy green vegetables (NHMRC 1991). With a standard healthy diet, intake of vitamin E would be up to 30 mg alpha-TE per day unless wheatgerm oil is a major dietary constituent (NHMRC 1991). Synthetic forms of vitamin E are also available and commonly used in vitamin preparations; however, these forms have less biological activity than their naturally occurring counterparts (IOM 2000).

Vitamin E deficiency is rarely seen in healthy adults and has primarily been characterised in preterm infants, low birthweight infants and those with fat malabsorption disorders. Reported symptoms of deficiency include haemolytic anaemia, reticulocytosis, hyperbilirubinaemia, low haemoglobin levels (Gross 1982) and peripheral neuropathy (Roberts 1990). Vitamin E deficiency is exacerbated in the presence of iron overload and a high dietary intake of polyunsaturated fatty acids (PUFAs), which is of particular relevance for preterm infants fed formula containing high levels of iron and PUFAs (Roberts 1990). Establishing a recommended dietary intake (RDI) of vitamin E has been impeded by the low observance of overt vitamin E deficiency; however, current RDI range from 7 mg to 10 mg alpha-TE (Roberts 1990). During pregnancy, losses of vitamin E to the fetus are thought to be minimal and thus the RDI during pregnancy is often unchanged (NHMRC 1991).

Vitamin E functions as an antioxidant in the lipid phase, protecting phospholipid fatty acids from oxidation by harmful free radicals (reactive oxygen molecules) and thus stabilising cell membranes. As an antioxidant, vitamin E helps to prevent oxidative stress, which is characterised by an excess of free radicals coupled with decreased antioxidants available to quench these free radicals. Vitamin E interacts synergistically with vitamin C, a water soluble antioxidant, where vitamin C helps to convert oxidised vitamin E back into a useful form (Packer 1979). This relationship may account for the limited observation of overt vitamin E deficiency in humans, as vitamin C may aid in recycling vitamin E stores. Vitamin E and vitamin C supplements are often given concurrently

to utilise this relationship and to promote antioxidant defences in both the aqueous and lipid phase. Little is known about other potential functions of vitamin E as research to date has focussed on its antioxidant properties. Doses of vitamin E required to have an antioxidant effect have been reported at least to 400 international units (approximately 268 mg alpha-TE) (Devaraj 1997).

Oxidative stress has been linked to the development of adult diseases including cardiovascular disease, cancer, chronic inflammation and neurologic disorders, resulting in many large multicentre clinical trials of vitamin E supplementation. The results of these large trials of vitamin E supplementation have been inconclusive, and benefits remain to be consistently reported (Brigelius-Flohe 2002). During pregnancy, oxidative stress has been implicated in the development of pre-eclampsia (Roberts 1990), and proposed in the disease processes of intrauterine growth restriction (Kingdom 2000) and prelabour rupture of membranes both preterm and at term (Woods 2001). Oxidative stress has also been implicated in many of the disorders common to preterm infants including chronic lung disease, intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotising enterocolitis and bronchopulmonary dysplasia (Saugstad 1988; Saugstad 2001). Preventing complications in pregnancy like pre-eclampsia, growth restriction, preterm premature rupture of membranes and serious neonatal morbidities would represent significant cost savings in hospital and intensive care unit admissions and the use of other healthcare resources. Other Cochrane reviews are assessing 'Antioxidants for preventing pre-eclampsia' (Rumbold 2005a) and 'Vitamin C supplementation in pregnancy' (Rumbold 2005b).

Vitamin E appears to have low toxicity in humans. However there is limited evidence on the safety of using vitamin E in pregnancy. Despite the lack of evidence on safety, the United States Institute of Medicine Food and Nutrition Board has set an upper tolerable limit of vitamin E ingestion in pregnancy at 1000 mg per day (IOM 2000), indicating the highest level of intake that is likely to pose no risk of adverse health effects to almost all women. In non-pregnant adults controlled clinical trials of vitamin E supplementation in a variety of doses have failed to demonstrate any consistent side-effects (Bendich 1993). Observational studies, however, have reported adverse effects including fatigue, weakness, creatinuria, dermatitis, reduced thyroid function, increased urinary androgen excretion, reduced leukocyte action and altered coagulation factors resulting in increased bleeding in vitamin K deficient individuals (Bendich 1993; Roberts 1990). The mechanisms leading to altered coagulation factors are unclear; however, vitamin E has been reported to potentiate the effect of anticoagulant therapy, such as warfarin. Newborn infants have a relative vitamin K deficiency at birth, hence vitamin E supplementation during pregnancy may influence the risk of vitamin K deficiency bleeding or haemorrhagic disease of the newborn unfavourably if vitamin K is not given at birth. In controlled trials of vitamin E supplementation in preterm infants for the treatment of retinopathy of prematurity, vitamin E supplementation has been associated with an increased risk of bacterial sepsis and necrotising enterocolitis (Johnson 1985). Given the lipid soluble nature of vitamin E, supplementation may result in increased storage of the vitamin in organs such as the liver, muscle and adipose tissue when used in high doses. The need to demonstrate the efficacy and safety of using vitamin E in pregnancy is particularly important when vitamin E is given in high doses.

The aims of this review are (i) to identify all published, unpublished randomised and quasi-randomised controlled trials investigating vitamin E supplementation in pregnancy and (ii) to investigate the benefits and hazards of vitamin E supplementation in pregnancy.

## OBJECTIVES

To assess, using the best available evidence, the effects of vitamin E supplementation, alone or in combination with other separate supplements, on pregnancy outcomes, adverse events, side-effects and use of health services.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All randomised or quasi-randomised controlled trials evaluating the effect of vitamin E supplementation in pregnant women.

#### Types of participants

Pregnant women receiving vitamin E supplementation or control, living in areas where there is either inadequate dietary intake of vitamin E or where there is presumed adequate intake.
Women were classified into subgroups where possible, based on:
(a) the dosage of the vitamin E supplement (above or equal to/ below the recommended dietary intake of 7 mg alpha-TE);
(b) the gestation at trial entry (trial entry less than 20 weeks or greater than or equal to 20 weeks);
(c) whether women have low or adequate dietary vitamin E intake prior to trial entry (low intake defined as intake less than the recommended dietary intake in that setting as measured by dietary questionnaire);
(d) the use of vitamin E in combination with other dietary supplements;
(e) women's risk status for adverse pregnancy outcomes (as defined by the trial authors).

### Types of interventions

Vitamin E supplementation, alone or in combination with other separate supplements compared with placebo, no placebo or other supplements. Interventions using a multivitamin supplement (more than two vitamins or minerals combined in the one tablet preparation) that contained vitamin E were excluded.

### Types of outcome measures

#### Primary outcomes

1. Stillbirth, neonatal death, perinatal death or infant death;
2. maternal and infant haematological measures: haemolytic anaemia, reticulocytosis, hyperbilirubinaemia and haemoglobin concentrations;
3. preterm birth (defined as less than 37 weeks' gestation);
4. development of clinical pre-eclampsia;
5. intrauterine growth restriction (defined as birthweight less than third centile or the most extreme centile reported);
6. birthweight;
7. prelabour rupture of fetal membranes, preterm and at term.

#### Secondary outcomes

For the mother: death up to six weeks postpartum, elective delivery (induction of labour or elective caesarean section), caesarean section (emergency plus elective), bleeding episodes (such as placental abruption, antepartum haemorrhage, postpartum haemorrhage, complications of epidural anaesthesia, need for transfusion), measures of serious maternal morbidity (such as eclampsia, liver failure, renal failure, disseminated intravascular coagulation, pulmonary oedema), peripheral neuropathy and maternal satisfaction with care.

For the child: gestational age at birth, congenital malformations, Apgar score less than seven at five minutes, vitamin K deficiency bleeding or haemorrhagic disease of the newborn, respiratory distress syndrome, chronic lung disease, periventricular haemorrhage, periventricular leukomalacia, bacterial sepsis, necrotising enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, peripheral neuropathy, disability at childhood follow up (such as cerebral palsy, intellectual disability, hearing disability and visual impairment) and poor childhood growth.

Adverse events related to vitamin E supplementation sufficient to stop supplementation.

Side-effects of vitamin E supplementation such as fatigue, weakness, altered coagulation times, immunosuppression, creatinuria, dermatitis, altered thyroid function and increased urinary androgen excretion.

#### Use of health service resources

For the woman: antenatal hospital admission, visits to day care units, use of intensive care, ventilation and dialysis.

For the infant: admission to special care/intensive care nursery, duration of mechanical ventilation, length of stay in hospital, as well as development and special needs after discharge.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group trials register by contacting the Trials Search Co-ordinator (23 June 2004). We updated this on 7 May 2010 and added the results to Studies awaiting classification.

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2004, Issue 2), MEDLINE (1966 to May 2004), Current Contents (1998 to May 2004) and EMBASE (1980 to May 2004) for potentially eligible studies, using the search strategies detailed in Appendix 1.

We did not apply any language restrictions.

## Data collection and analysis

Two authors assessed potentially eligible trials found after the literature search for their suitability for inclusion in the review. Decisions regarding inclusion were made separately and results compared. We resolved any disagreement through discussion. Two authors extracted data using an agreed format, and again we resolved

discrepancies through discussion. We entered data separately and double checked them.

We assessed the validity of each included trial according to the criteria outlined in the Cochrane Reviewers' Handbook (Clarke 2000). We assessed trials with a grade allocated to each trial on the basis of allocation concealment: A (adequate), B (unclear) or C (clearly inadequate). Where the method of allocation concealment was unclear, we made attempts to contact authors to provide further details.

We assessed blinding, completeness of follow up and use of placebo for each outcome using the following criteria.

#### For blinding of assessment of outcome

A. Double blind, neither investigator, the outcome assessor nor participant knew or were likely to guess the allocated treatment;
B. single blind, either the investigator or the participant knew the allocation; or, the trial is described as double blind, but side-effects of one or other treatment mean that it is likely that for a significant proportion (at least 20%) of participants the allocation could be correctly identified;
C. no blinding, where the investigator, outcome assessor and participant knew (or were likely to guess) the allocated treatment;
D. unclear.

#### For completeness of follow up

A. Less than 3% of participants excluded;
B. 3% to 9.9% of participants excluded;
C. 10% to 19.9% of participants excluded;
D. excluded: greater than or equal to 20% of participants excluded.

#### For use of placebo control

A. Placebo controlled;
B. unclear whether placebo controlled;
C. no placebo control.

We carried out statistical analyses using the Review Manager software (RevMan 2004) with results presented as summary relative risk. We applied tests of heterogeneity between trials to assess the significance of any differences between trials ($I^2$ greater than or equal to 50%) and explored possible causes of heterogeneity. We calculated summary relative risks using a fixed-effect model. If heterogeneity was detected, we performed subgroup analyses for the main outcomes by vitamin E dosage, gestation at trial entry, prior dietary intake of vitamin E, use of vitamin E in combination with other supplements, and women's risk status of adverse pregnancy outcomes as defined by the authors. Heterogeneity that was not explained by subgroup analyses was modelled using random-effects analysis.

We included all included trials in the initial analyses and carried out sensitivity analyses to explore the effect of trial quality. This involved analysis based on an A, B or C rating of allocation concealment, blinding of assessment of outcome, completeness of follow up and placebo control. We compared the results of high-quality studies with those of poorer quality studies, where studies rated A for all quality criteria were compared with those rated B or C.

## RESULTS

### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

*See* tables 'Characteristics of included studies' and 'Characteristics of excluded studies' for details of individual studies.

We identified four trials involving 566 women as eligible for inclusion in the review. Of these, three trials assessed vitamin E supplementation for the prevention of pre-eclampsia (Beazley 2002; Chappell 1999; Rivas 2000). One trial assessed vitamin E supplementation for the prevention of serious maternal complications and iatrogenic preterm birth in women with established early onset pre-eclampsia (Gulmezoglu 1997).

Six studies were excluded, either because no clinically meaningful data were reported in a format suitable for inclusion (Anthony 1996; Pressman 2003; Sawhney 2000) or the studies were non-randomised (Bolisetty 2002; Lietz 2001; Moldenhauer 2002).

(Twenty-three reports from an updated search in May 2010 have been added to Studies awaiting classification.)

#### Participants

Three trials recruited women who were at "high risk of pre-eclampsia" (Beazley 2002; Chappell 1999; Rivas 2000). The criteria for women being at high risk varied between trials, and included: previous pre-eclampsia, chronic hypertension, insulin-requiring diabetes mellitus or multiple gestation (Beazley 2002); abnormal doppler waveform in either uterine artery at 18 to 22 weeks' gestation or a history in the preceding pregnancy of pre-eclampsia necessitating delivery before 37 weeks' gestation, eclampsia or the syndrome of haemolysis, elevated liver enzymes, low platelets (Chappell 1999); or nulliparity, previous pre-eclampsia, obesity, hypertension, less than 20 years old, diabetes, nephropathy, mean arterial presion above of 85 mmHg, positive roll-over test, black race, family history of hypertension or pre-eclampsia, twin pregnancy and poor socioeconomic conditions (Rivas 2000). The fourth trial involved women with established severe early onset pre-eclampsia (Gulmezoglu 1997). The timing of commencement of supplementation differed widely, one trial enrolled women between 14 and 20 weeks' gestation (Beazley 2002), while others enrolled women between 16 and 22 weeks' gestation (Chappell 1999), 24 to 32 weeks' gestation (Gulmezoglu 1997) or any women below 29 weeks' gestation (Rivas 2000).

### Interventions

All of the four trials gave women supplements with vitamin E in addition to vitamin C. Two trials supplemented women with additional supplements, either allopurinol (Gulmezoglu 1997) or aspirin and fish oil (Rivas 2000). Three trials used the same dose of daily 400 international units (IU) vitamin E (Beazley 2002; Chappell 1999; Rivas 2000) and the fourth trial gave women daily 800 IU vitamin E (Gulmezoglu 1997).

### Outcomes

#### Primary outcomes

Few trials reported many of the primary or secondary outcomes. Stillbirth was reported by two trials (Chappell 1999; Gulmezoglu 1997), neonatal death and perinatal death by one trial (Gulmezoglu 1997) and no trials reported any data for infant deaths. No trials reported any data on maternal and infant haematological measures including haemolytic anaemia, reticulocytosis, hyperbilirubinaemia and haemoglobin concentrations. For the other primary outcomes, two trials reported preterm birth (Beazley 2002; Chappell 1999); three trials reported pre-eclampsia (Beazley 2002; Chappell 1999; Rivas 2000); two trials reported intrauterine growth restriction as birthweight less than the 10th centile for gestational age (Beazley 2002; Chappell 1999); one trial reported mean birthweight in a format suitable for inclusion in the review (Beazley 2002); and two trials reported median birthweight and range or interquartile range (Chappell 1999; Gulmezoglu 1997). No trials reported prelabour rupture of membranes either preterm or at term.

#### Secondary outcomes

One trial reported maternal death (Gulmezoglu 1997), one trial reported prelabour caesarean section (Gulmezoglu 1997), two trials reported placental abruption (Chappell 1999; Gulmezoglu 1997) and one trial reported measures of serious maternal morbidity including eclampsia, renal failure, disseminated intravascular coagulation and pulmonary oedema (Gulmezoglu 1997). One trial reported gestational age at birth (Beazley 2002) and one trial reported Apgar score less than seven at five minutes (Gulmezoglu 1997).

No trials reported maternal or infant peripheral neuropathy, maternal satisfaction with care, congenital malformations, vitamin K deficiency bleeding or haemorrhagic disease of the newborn, respiratory distress syndrome, chronic lung disease, periventricular haemorrhage or leukomalacia, bacterial sepsis, necrotising enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, disability at childhood follow up, poor childhood growth or any adverse events related to vitamin E supplementation.

One trial reported side-effects of vitamin E supplementation, neonatal admission to the intensive care unit, and the need for mechanical ventilation (Gulmezoglu 1997). No trials reported any data for maternal use of health resources.

## Risk of bias in included studies

### Allocation concealment

Formal randomisation was reported in two trials by use of third party randomisation (Chappell 1999; Gulmezoglu 1997). For the remaining two trials (Beazley 2002; Rivas 2000), the degree of concealment was unclear; both were reported as abstracts and gave no information about methods of randomisation.

### Blinding

Two trials explicitly stated that women, caregivers and researchers were blinded to treatment allocations (Chappell 1999; Gulmezoglu 1997). One trial stated "double-blind" in the text (Beazley 2002) while the other trial used the term "triple-blind" in the text (Rivas 2000).

### Completeness of follow up

Three trials either reported outcomes for all randomised women according to treatment allocation (Chappell 1999) or did not state any losses to follow up (Gulmezoglu 1997; Rivas 2000). One trial (Beazley 2002) reported nine women (eight per cent) were lost to follow up.

### Use of placebo

All four trials used a placebo. The content of the placebo used was explicitly stated for one trial (microcrystalline cellulose and soya bean oil) (Chappell 1999), however no details of the placebo preparation were disclosed for the remaining three trials (Beazley 2002; Gulmezoglu 1997; Rivas 2000).

## Effects of interventions

Four trials, involving 566 women, are included.

### Primary outcomes

No difference was found between women supplemented with vitamin E in combination with other supplements compared with placebo for the risk of stillbirth (relative risk (RR) 0.77, 95% confidence intervals (CI) 0.35 to 1.71, two trials, 339 women (Chappell 1999; Gulmezoglu 1997)), neonatal death (RR 5.00,

95% CI 0.64 to 39.06, one trial, 40 women (Gulmezoglu 1997)) or perinatal death (RR 1.29, 95% CI 0.67 to 2.48, one trial, 56 women (Gulmezoglu 1997)), using fixed-effect models. No trials reported the outcomes infant death, haemolytic anaemia, reticulocytosis, hyperbilirubinaemia or maternal or infant haemoglobin concentrations.

No difference was demonstrated in the risk of preterm birth between women supplemented with vitamin E in combination with other supplements compared with placebo (RR 1.29, 95% CI 0.78 to 2.15, two trials, 383 women (Beazley 2002; Chappell 1999)).

Women supplemented with vitamin E in combination with other supplements compared with placebo were at decreased risk of developing clinical pre-eclampsia (RR 0.44, 95% CI 0.27 to 0.71, three trials, 510 women (Beazley 2002; Chappell 1999; Rivas 2000)), using a fixed-effect model. However, substantial heterogeneity was found for pre-eclampsia. When using a random-effects model, a difference in the risk of pre-eclampsia between treatment groups could not be demonstrated (RR 0.44, 95% CI 0.16 to 1.22, three trials, 510 women (Beazley 2002; Chappell 1999; Rivas 2000)).

No difference was found for the risk of intrauterine growth restriction (RR 0.72, 95% CI 0.49 to 1.04, two trials, 383 women (Beazley 2002; Chappell 1999)) or birthweight (weighted mean difference (WMD) -139.00 g, 95% CI -517.68 to 239.68, one trial, 100 women (Beazley 2002)), between women supplemented with vitamin E in combination with other supplements compared with placebo. No trials provided data on prelabour rupture of membranes either preterm or at term.

### Secondary outcomes

One trial (Gulmezoglu 1997) reported that there were no maternal deaths in either treatment arm. There was no difference between women supplemented with vitamin E in combination with other supplements compared with placebo for prelabour caesarean section (RR 1.51, 95% CI 0.86 to 2.63, one trial, 55 women (Gulmezoglu 1997)), placental abruption (RR 0.35, 95% CI 0.10 to 1.23, two trials, 339 women (Chappell 1999; Gulmezoglu 1997)), eclampsia (RR 1.07, 95% CI 0.07 to 16.33, one trial, 56 women (Gulmezoglu 1997)), renal failure (RR 0.36, 95% CI 0.02 to 8.41, one trial, 56 women (Gulmezoglu 1997)), disseminated intravascular coagulation (RR 0.36, 95% CI 0.02 to 8.41, one trial, 56 women (Gulmezoglu 1997)), pulmonary oedema (RR 0.54, 95% CI 0.05 to 5.59, one trial, 56 women (Gulmezoglu 1997)), gestational age at birth (WMD -0.40 weeks, 95% CI -1.87 to 1.07, one trial, 100 women (Beazley 2002)) or Apgar score less than seven at five minutes (RR 0.63, 95% CI 0.21 to 1.90, one trial, 39 women (Gulmezoglu 1997)).

No trials reported maternal or infant peripheral neuropathy, maternal satisfaction with care, congenital malformations, vitamin K deficiency bleeding or haemorrhagic disease of the newborn, respiratory distress syndrome, chronic lung disease, periventricular haemorrhage or leukomalacia, bacterial sepsis, necrotising enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, disability at childhood follow up, poor childhood growth or any adverse events related to vitamin E supplementation.

One trial reported side-effects of supplementation with vitamin E in combination with other supplements. However, there was no difference in the risk of developing acne (RR 3.21, 95% CI 0.14 to 75.68, one trial, 56 women (Gulmezoglu 1997)), transient weakness (RR 5.36, 95% CI 0.27 to 106.78, one trial, 56 women (Gulmezoglu 1997)) or skin rash (RR 3.21, 95% CI 0.14 to 75.68, one trial, 56 women (Gulmezoglu 1997)) between treatment groups. For women supplemented with vitamin E in combination with other supplements compared with placebo, there was no difference in the number of infants admitted to the intensive care unit (RR 0.83, 95% CI 0.30 to 2.29, one trial, 40 infants (Gulmezoglu 1997)) or requiring mechanical ventilation (RR 0.33, 95% CI 0.08 to 1.46, one trial, 40 infants (Gulmezoglu 1997)). No data for maternal use of health resources were reported by any of the trials.

### Sensitivity analyses by trial quality

Assessments of the treatment effects were made for the primary outcomes based on trial quality. Two trials (Chappell 1999; Gulmezoglu 1997) fulfilled the highest criteria for all of the quality measures, that is they were rated 'A' for allocation concealment, had no losses to follow up, involved blinding of women, caregivers and researchers and used placebo control. Two trials did not fulfil the highest criteria for all of the quality measures (Beazley 2002; Rivas 2000) and these trials were excluded from the analyses. For the outcomes stillbirth, neonatal death and perinatal death, all included trials were of high quality (Chappell 1999; Gulmezoglu 1997). There was no difference between women supplemented with vitamin E compared with placebo for the risk of stillbirth (RR 0.77, 95% CI 0.35 to 1.71, two trials, 339 women (Chappell 1999; Gulmezoglu 1997)), neonatal death (RR 5.00, 95% CI 0.64 to 39.06, one trial, 40 women (Gulmezoglu 1997)) or perinatal death (RR 1.29, 95% CI 0.67 to 2.48, one trial, 56 women (Gulmezoglu 1997)).

When trials not rated high quality were excluded from the analyses, the risk of preterm birth, pre-eclampsia and intrauterine growth restriction did not change; however, the confidence intervals around the relative risks changed slightly. No difference was seen for the risk of preterm birth between women supplemented with vitamin E compared with placebo (RR 1.21, 95% CI 0.38 to 3.87, one trial, 283 women (Chappell 1999)). For the outcome pre-eclampsia, women supplemented with vitamin E compared with placebo were at lower risk of pre-eclampsia (RR 0.46, 95% CI 0.24 to 0.91, one trial, 283 women (Chappell 1999)), using a random-effects model. There was no difference in the risk of intrauterine growth restriction for women supplemented with vitamin E com-

pared with placebo (RR 0.74, 95% CI 0.50 to 1.08, one trial, 283 women (Chappell 1999)). The only trial reporting birthweight was not rated high quality (Beazley 2002).

### Subgroup analyses

#### Dosage of the vitamin E supplement (above or equal to/below the recommended dietary intake of 7 mg alpha-TE)

All of the included studies supplemented women with vitamin E in a dosage above the recommended dietary intake. Three trials (Beazley 2002; Chappell 1999; Rivas 2000) supplemented women with daily 400 international units (IU) vitamin E, and one trial (Gulmezoglu 1997) supplemented women with daily 800 IU vitamin E. Because of the lack of variation in dosage between trials, subgroup analyses based on dosage were not performed.

#### Gestation at trial entry (less than 20 weeks or greater than or equal to 20 weeks)

One trial (Beazley 2002) enrolled women from less than or equal to 20 weeks' gestation; one trial (Gulmezoglu 1997) enrolled women after 20 weeks' gestation; and the other trials (Chappell 1999; Rivas 2000) enrolled women both before and after 20 weeks' gestation. There was no difference in the risk of stillbirth between women supplemented with vitamin E compared with placebo after 20 weeks' gestation (RR 0.84, 95% CI 0.36 to 1.93, one trial, 56 women (Gulmezoglu 1997)) or women supplemented both before and after 20 weeks' gestation (RR 0.50, 95% CI 0.05 to 5.49, one trial, 283 women (Chappell 1999)). There were no data on stillbirth for the trial supplementing women before 20 weeks' gestation. For preterm birth, there was no difference in the risk of preterm birth between women supplemented with vitamin E compared with placebo before to 20 weeks' (RR 1.32, 95% CI 0.75 to 2.31, one trial, 100 women (Beazley 2002)) or for women supplemented both before and after 20 weeks' gestation (RR 1.21, 95% CI 0.38 to 3.87, one trial, 283 women (Chappell 1999)). There were no data on preterm birth for the trial supplementing women after 20 weeks' gestation. There was no difference in the risk of pre-eclampsia between women supplemented with vitamin E compared with placebo before 20 weeks' gestation (RR 0.92, 95% CI 0.40 to 2.13, one trial, 100 women (Beazley 2002)) or for women supplemented both before and after 20 weeks' gestation (RR 0.23, 95% CI 0.04 to 1.46, two trials, 410 women (Chappell 1999; Rivas 2000)), using random-effects models. Similarly, there was no difference in the risk of intrauterine growth restriction between women supplemented with vitamin E compared with placebo before 20 weeks' gestation (RR 0.46, 95% CI 0.09 to 2.41, one trial, 100 women (Beazley 2002)), or both before and after 20 weeks' gestation (RR 0.74, 95% CI 0.50 to 1.08, one trial, 283 women (Chappell 1999)). There were no data on intrauterine growth restriction for the trial supplementing women after 20 weeks' gestation.

#### Low or adequate dietary vitamin E intake prior to trial entry (low intake defined as intake less than the recommended dietary intake in that setting as measured by dietary questionnaire)

None of the trials reported any information on women's dietary intake of vitamin E prior to trial entry or during the trial. No subanalyses could therefore be performed.

#### The use of vitamin E in combination with other dietary supplements

None of the trials supplemented women with vitamin E alone. All of the trials gave vitamin E in addition to vitamin C, and two trials also supplemented women additionally with either allopurinol (Gulmezoglu 1997) or aspirin and fish oil (Rivas 2000). Subgroup analyses based on the use of vitamin E alone or with other supplements were therefore not performed.

#### Women's risk status for adverse pregnancy outcomes (as defined by the authors)

Three trials supplemented women who were at high risk of pre-eclampsia (Beazley 2002; Chappell 1999; Rivas 2000) and the fourth trial supplemented women who had established early onset pre-eclampsia. Hence all women were classified as high risk for adverse pregnancy outcomes, and subgroup analyses based on women's risk of adverse pregnancy outcomes were unable to be performed.

## DISCUSSION

We cannot support routine vitamin E supplementation alone or in combination with other supplements or drugs in pregnancy. From the limited trials reviewed there are insufficient data for reliable conclusions about vitamin E supplementation in pregnancy. The total number of women involved in the included trials was small (566 in total), and two trials were of poor quality and published in abstract form only. All of the women involved in the trials were either at high risk of pre-eclampsia or had established severe early onset pre-eclampsia. There was no information available to assess whether vitamin E supplementation may be useful for all pregnant women. Similarly, all of the included trials assessed vitamin E supplementation in combination with vitamin C and other supplements including allopurinol or aspirin and fish oil. There was no information available to assess whether vitamin E supplementation alone may be beneficial for women, hence any

treatment effects seen here may not be directly attributable to vitamin E. For further information on vitamin C supplementation see the Cochrane review 'Vitamin C supplementation in pregnancy' (Rumbold 2005b). Trials of combined vitamin C and vitamin E supplementation have been included in both reviews.

There was no information available to evaluate the impact of vitamin E supplementation on important outcomes such as infant death, measures of maternal and infant haematological status, prelabour rupture of membranes (either preterm or term), serious infant morbidities or maternal satisfaction with care. Similarly, for the outcomes that were reported, not all trials reported all of these outcomes, which creates the potential for bias and limits the reliability of the results.

Substantial heterogeneity was detected for the outcome pre-eclampsia. When poor quality trials were excluded from the analyses, women supplemented with vitamin E had a reduced risk of pre-eclampsia. Caution must be taken when interpreting this finding as only one high-quality trial reported on pre-eclampsia, and the number of women included in this trial was small. No firm conclusions should be drawn from results of single trials with small sample sizes. The role of vitamin E and other antioxidants in the prevention of pre-eclampsia is being further explored in the Cochrane Review 'Antioxidants for preventing pre-eclampsia' (Rumbold 2005a). Further trials evaluating the role of vitamin E supplementation in preventing pre-eclampsia are warranted for women at high risk and low risk of pre-eclampsia.

One trial involving 56 women reported potential side-effects of vitamin E supplementation, including acne, transient weakness and skin rash. None of these outcomes were reported by any of the women in the placebo group, however, the differences between treatment groups for these outcomes were not statistically significant. No other trials reported any potential side-effects or adverse effects of vitamin E supplementation.

# AUTHORS' CONCLUSIONS

## Implications for practice

From the limited trials reviewed, the data do not support routine vitamin E supplementation either alone or in combination with other supplements in pregnancy, for all women or women at high risk of pregnancy complications. The data are too few to produce any reliable conclusions about any benefits or harms of supplementation.

## Implications for research

There is currently no information available to assess any benefits or harms of supplementing women during pregnancy with vitamin E alone. The role of vitamin E supplementation either alone or with other supplements such as vitamin C, aspirin and fish oil in preventing pre-eclampsia needs to be further explored, for women at high- and low-risk of pre-eclampsia. Future trials assessing vitamin E supplementation should be of high quality and large enough to assess pre-eclampsia and other serious maternal and infant morbidities. Future trials should collect information on maternal satisfaction with care, side-effects and adverse effects for the mother and infant, including vitamin K deficiency bleeding in the infant, and trials should involve long-term follow up to ensure an accurate evaluation of the safety of vitamin E supplementation.

[Note: The 24 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

# ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Beazley 2002**

| | |
|---|---|
| Methods | Treatment allocation: unclear, no methodological details given, women were "randomised"<br>Blinding of outcome assessment: "double blind" stated.<br>Documentation of exclusion: 9 (8%) women were lost to follow up<br>Use of placebo control: placebo control. |
| Participants | 109 women were recruited into the study. Inclusion criteria: women at "high risk of pre-eclampsia" including those with previous pre-eclampsia, chronic hypertension, pregestational diabetes and multiple pregnancy. Nil exclusion criteria stated. Women were randomised at 14-20 weeks' gestation to receive either daily vitamin E and C (n = 54) or placebo (n = 55) |
| Interventions | Women randomised to the treatment group received daily 400 IU vitamin E in addition to 1000 mg vitamin C. No details on the content of the placebo were given |
| Outcomes | 1. Pre-eclampsia (not defined).<br>2. GA at delivery (weeks).<br>3. Preterm birth (< 37 weeks' gestation).<br>4. Birthweight.<br>5. Birthweight < 10 centile.<br>6. Total antioxidant status and 8-isoprostane. |
| Notes | Dosage: daily 400 IU vitamin E, above RDI.<br>Gestational age at trial entry: <= 20 weeks' gestation.<br>Dietary vitamin E intake before trial entry: unclear, no dietary information reported<br>Type of supplement: vitamin E given in addition to vitamin C<br>Women's risk status: women were at high risk of pre-eclampsia<br>Intention to treat analyses: stated that analyses were intention to treat, however losses to follow up were not included in the totals. Available case analysis<br>Sample size calculation: none reported.<br>Compliance: unclear, no details given.<br>Location: United States of America.<br>Timeframe: unclear.<br>Published in abstract format only. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Chappell 1999**

| | |
|---|---|
| Methods | Treatment allocation: a computer-generated randomisation list using blocks of ten was given to the hospital pharmacy departments. Researchers allocated the next available number to participants and women collected the trial tablets from the pharmacy department<br>Blinding of outcome assessment: women, caregivers and researchers were blinded to the treatment allocation until recruitment, data collection and laboratory analyses were complete<br>Documentation of exclusion: Pregnancy outcome data were reported according to treatment allocation for all women randomised<br>Use of placebo control: placebo control. |
| Participants | 283 women were recruited into the study. Inclusion criteria: abnormal Doppler waveform in either uterine artery at 18-22 weeks' gestation or a history in the preceding pregnancy of pre-eclampsia necessitating delivery before 37 weeks' gestation, eclampsia or the syndrome of HELLP.<br>Exclusion criteria: heparin or warfarin treatment, abnormal fetal-anomaly scan or multiple pregnancy.<br>Women were randomised at 18-22 weeks' gestation; however, women with a previous history who were identified at an earlier stage were randomised at 16 weeks' gestation. Women with abnormal Doppler waveform analysis returned for a second scan at 24 weeks' gestation, those with a normal waveform at this time stopped treatment and were withdrawn from the study. The remaining women who had persistently abnormal waveforms and those with a previous history or pre-eclampsia remained in the study and were seen every 4 weeks through the rest of pregnancy. 1512 women underwent Doppler screening, 273 women had abnormal waveforms and, of these, 242 women consented to the study. An additional 41 women who had a history of pre-eclampsia consented. 283 women were randomised to either the vitamin C and E group (n = 141) or the placebo group (n = 142), 72 women had normal Doppler scans at 24 weeks' gestation and 24 women did not return for a second scan and were withdrawn. A further 27 women withdrew from the trial after 24 week's gestation for various reasons. In total, 160 women completed the trial protocol until delivery, 79 in the vitamin C and E group and 81 in the placebo group. Pregnancy outcome data were presented for all women randomised (n = 283) as well as only for those women completing the trial protocol (n = 160) |
| Interventions | Women randomised to the vitamin E and C group received capsules containing 400 IU natural source vitamin E daily and tablets containing 1000 mg vitamin C daily. Women randomised to the placebo group received capsules containing soya bean oil and tablets containing microcrystalline cellulose that were identical in appearance to the vitamin E capsules and vitamin C tablets.<br>After 24 weeks' gestation women were seen every 4 weeks, and blood samples were taken at each visit |
| Outcomes | 1. Ratio of PAI-1 to PAI-2.<br>2. Incidence of pre-eclampsia (defined according to the International Society for the Study of Hypertension in Pregnancy guidelines).<br>3. Placental abruption.<br>4. Spontaneous preterm delivery (< 37 weeks' gestation).<br>5. Intrauterine death.<br>6. Small-for-gestational-age infants (on or below the 10th centile).<br>7. Mean systolic and diastolic blood pressure before delivery.<br>8. Gestational age at delivery (median, IQR).<br>9. Birthweight (median, IQR).<br>10. Birthweight centile (median, IQR).<br>11. Mean plasma ascorbic acid and alpha-tocopherol concentrations during gestation.<br>12. Biochemical indices of oxidative stress and placental function |

**Chappell 1999** (*Continued*)

| | |
|---|---|
| Notes | Dosage: 400 IU natural source vitamin E daily, above RDI.<br>GA at trial entry: between 16-22 weeks' gestation.<br>Dietary vitamin E intake before trial entry: unknown, not assessed<br>Type of supplement: vitamin E given in addition to vitamin C<br>Women's risk status: women were at "high risk for pre-eclampsia"<br>Intention to treat analyses: performed, pregnancy outcome data were available for all women randomised, and results were presented according to initial treatment allocation<br>Sample size calculation: the study had 80% power to detect a 30% reduction in PAI-1<br>Compliance: not specifically reported. "Within the treated group, plasma ascorbic acid concentration increased by 32% from baseline values and plasma alpha-tocopherol increased by 54%."<br>Location: London, United Kingdom.<br>Timeframe: unclear. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Gulmezoglu 1997**

| | |
|---|---|
| Methods | Treatment allocation: "The treatment packs were randomised by computer generated random numbers in blocks of ten". Randomisation was carried out by an independent researcher who was not involved in the study, and medications were placed in consecutively numbered sealed opaque bags<br>Blinding of outcome assessment: women, caregivers and researchers were blinded to the treatment allocation<br>Documentation of exclusion: no exclusions documented.<br>Use of placebo control: placebo control. |
| Participants | 56 women were recruited into the study. Inclusion criteria: women who were admitted to the antenatal wards with a diagnosis of severe pre-eclampsia, as defined by 2+ proteinuria on urine dipstix testing (in at least two consecutive tests 4 to 6 hours apart), with a blood pressure of 160/110 mmHg, or 3+ proteinuria with blood pressure >= 150/100 mmHg; between 24 and 32 weeks' gestation; with a single live fetus; with no systemic disorder (such as diabetes or systemic lupus erythematosus) and no allergy to study medications. Women were approached when they were eligible for conservative management, as defined by an absence of significant renal impairment, the HELLP syndrome or thrombocytopenia alone. Conservative management consisted of advising women to stay in hospital until delivery, with weekly betamethasone injections up to 32-34 weeks' gestation, and with frequent fetal and maternal monitoring.<br>Exclusion criteria: none stated.<br>59 women were approached and counseled about the study, of which 56 women gave informed written consent, and allocated to either the vitamin group (n = 27) or placebo (n = 29) |
| Interventions | Women randomised to the vitamin group received twice daily 400 IU vitamin E (800 IU daily total), 500 mg vitamin C (1000 mg daily total) and 100 mg allopurinol (200 mg daily total). Women randomised to the placebo group received the same number of tablets that were identical to the vitamin C and allopurinol tablets. Vitamin C placebos were used as placebos for vitamin E because it was not possible to obtain two separate sets of placebos from the supplier; however, the vitamin E tablets and their placebos were slightly different. To preserve blinding all medications were placed in dark brown coloured bottles and |

**Gulmezoglu 1997** (*Continued*)

| | |
|---|---|
| | sealed opaque paper bags |
| Outcomes | 1. Delivery within 14 days.<br>2. Maternal deaths.<br>3. Serious maternal complications (pulmonary oedema, eclampsia, HELLP syndrome, disseminated intravascular coagulation, renal failure).<br>4. Placental abruption.<br>5. Prelabour caesarean section.<br>6. Use of antihypertensives.<br>7. Stillbirth.<br>8. Apgar score < 7 at 1 minute and < 7 at 5 minutes.<br>9. Umbilical artery pH < 7.2.<br>10. Admission to intensive care unit.<br>11. Mechanical ventilation.<br>12. Neonatal death.<br>13. Perinatal death.<br>14. Birthweight (median, range).<br>15. Lipid peroxide and vitamin E levels.<br>16. Haematological and renal function parameters.<br>17. Placental lipid peroxide and glutathione levels. |
| Notes | Dosage: 800 IU vitamin E, above RDI.<br>GA at trial entry: > 20 weeks' gestation.<br>Dietary vitamin E intake before trial entry: unclear, no dietary information reported<br>Type of supplement: vitamin E given in addition to vitamin C and allopurinol<br>Women's risk status: women had established early onset severe pre-eclampsia<br>Intention to treat analyses: all data were reported according to women's treatment allocation, and were available for all women for the primary outcome. There were missing data for the outcomes Apgar score < 7 at 1 minute, Apgar score < 7 at 5 minutes, umbilical artery pH < 7.2, and the lipid peroxide and vitamin E levels and haematological and renal function parameters<br>Sample size calculation: a sample size of 54 women had 80% power to detect a halving in the number of women needing delivery within 14 days, from 80% to 40%<br>Compliance: compliance in the vitamin group was estimated at 84%, 89%, 93% for the vitamin E, vitamin C and allopurinol tablets. For the placebo group compliance was 75%, 100% and 86% for the vitamin E, vitamin C and allopurinol placebo tablets<br>Location: Johannesburg, South Africa.<br>Timeframe: unclear. |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Rivas 2000**

| | |
|---|---|
| Methods | Treatment allocation: unclear, women were "randomly divided into two sub-groups"<br>Blinding of outcome assessment: "triple blind" stated.<br>Documentation of exclusion: none stated.<br>Use of placebo control: placebo control. |
| Participants | 127 women were recruited into the study. Inclusion criteria: women less than 29 weeks' gestation and with "high risk for pre-eclampsia", including any of the following factors: nulliparity, previous pre-eclampsia, obesity, hypertension, less than 20 years old, diabetes, nephropathy, mean arterial presion above of 85 mmHg, positive roll-over test, black race, family history of hypertension or pre-eclampsia, twin pregnancy and poor socioeconomic conditions.<br>Exclusion criteria: unclear, none stated. 127 women were allocated to vitamins C and E, aspirin and fish oil (n = 63) or placebo (n = 64) |
| Interventions | Women allocated to the treatment group received 400 IU vitamin E per day, 500 mg vitamin C per day, 100 mg aspirin three times a week and 1 g fish oil three times a day.<br>Women allocated to the placebo group, received placebo "at the same posology and presentation" |
| Outcomes | 1. Pre-eclampsia (not defined).<br>2. The authors report that "no serious maternal and neonatal side effects of treatment occurred in either group", no other details were given |
| Notes | Dosage: daily 400 IU vitamin E, above RDI.<br>GA at trial entry: unclear, "less than 29 weeks".<br>Dietary vitamin E intake before trial entry: unclear, no dietary information reported<br>Type of supplement: vitamin E in addition to vitamin C, aspirin and fish oil<br>Women's risk status: women were at "high risk for pre-eclampsia"<br>Intention to treat analyses: unclear, no details given.<br>Sample size calculation: unclear, reported as an abstract only<br>Compliance: no details given.<br>Location: Merida, Venezuela.<br>Timeframe: unclear, no details given.<br>Published in abstract format only. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

GA: gestational age
HELLP: haemolysis, elevated liver enzymes, low platelets
IQR: interquartile range
IU: international units
PAI-1: plasminogen activator inhibitor-1
PAI-2: plasminogen activatory inhibitor-2
RDI: recommended dietary intake

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Anthony 1996 | No clinical outcomes reported. Randomised controlled trial or seventy-three women undergoing conservative management of pre-eclampsia were supplemented with vitamin E (no dose information available). The abstract reported no differences in any of the clinical outcomes between the treatment groups; however, no other details were given. There are no further publications and no other information is available (personal communication with Prof J Anthony, August 2004) |
| Bolisetty 2002 | Not a randomised trial, pilot case control study. Twelve women at risk of preterm birth and between 30 and 36 week's gestation were given daily 20 mg beta-carotene, 167.8 mg vitamin E and 1000 mg vitamin C or acted as controls. Biochemical assessments of oxidative stress and maternal plasma concentrations of beta-carotene, vitamin E and vitamin C were reported |
| Lietz 2001 | Not a randomised trial. Women were supplemented with either red palm oil (a source of vitamin A), sunflower oil (a source of vitamin E) or acted as control. Allocation to treatment groups was "based on practicality". Reported outcomes included measures of plasma and breast milk vitamin A status, maternal haemoglobin and maternal weight |
| Moldenhauer 2002 | No clinical outcomes reported. Women in this study were participating in a randomised placebo controlled trial of calcium supplementation, and completed a dietary assessment at 12-21 weeks' gestation and 29-31 weeks' gestation. Women were not randomised to vitamin E supplementation. Unclear whether all women took a standard prenatal multivitamin or just women in the placebo group. Results are presented according to "teens", "twins" and "singleton" pregnancies, not according to whether women took the supplement or not. Outcomes reported included dietary intakes of vitamin C and E (with and without the contribution of the prenatal vitamin supplement). Published in abstract form only |
| Pressman 2003 | No clinical outcomes reported. Randomised controlled trial supplementing women with daily 500 mg vitamin C and 400 IU vitamin E from 35 weeks' gestation. Maternal plasma concentrations and amniotic fluid concentrations of vitamin C and E reported |
| Sawhney 2000 | No clinical outcomes reported. Randomised controlled trial of sixty women with established pre-eclampsia allocated to either vitamin E (no dose information given) or control. Reported outcomes were lipid peroxide and alpha-tocopherol levels and the percentage of women whose pregnancy continued for more than 14 days. No other information given. Published in abstract format only |

IU: international units

## Characteristics of ongoing studies *[ordered by study ID]*

**ACTS**

| | |
|---|---|
| Trial name or title | Australian Collaborative Trial of Supplements with vitamin C and vitamin E for the prevention of pre-eclampsia: a randomised controlled trial |
| Methods | |
| Participants | Inclusion criteria:<br>nulliparous women with a singleton pregnancy, between 14 + 0 and 21 + 6 weeks' gestation, with normal blood pressure, expecting to give birth at the collaborating centre, with no contraindication to vitamin C or E therapy and giving informed written consent<br>Exclusion criteria:<br>women with a multiple pregnancy, life threatening fetal anomaly on ultrasound, known thrombophilia, chronic renal failure, haemochromatosis or on heparin, warfarin or antihypertensive therapy |
| Interventions | Daily 1000 mg vitamin C and 400 IU vitamin E or placebo. |
| Outcomes | Primary outcomes:<br>Incidence of:<br>1. small-for-gestational-age infants.<br>2. clinical pre-eclampsia.<br>3. death or serious adverse outcome for the infant. |
| Starting date | December 2001. |
| Contact information | Prof. C Crowther<br>Ms A Rumbold,<br>Department of Obstetrics and Gynaecology, The University of Adelaide.<br>Email: acts@adelaide.edu.au |
| Notes | |

**DAPIT 2004**

| | |
|---|---|
| Trial name or title | The Diabetes and Pre-eclampsia Intervention Trial (DAPIT). |
| Methods | |
| Participants | Inclusion criteria:<br>Type 1 diabetes preceding pregnancy; age >= 16 years; between 8 and 22 weeks' gestation; date of last menstrual period certain and/or ultrasound estimation from 6-22 weeks of gestational age is available; singleton pregnancy.<br>Exclusion criteria:<br>ingestion of preparations containing vitamin C > 500 mg/day or vitamin E > 200 IU/day; participation in another study which may interfere with DAPIT; participation in DAPIT during a previous pregnancy, where DAPIT trial medication was taken within the last 6 months; any notation of drug abuse: cocaine, LSD, heroin, marijuana, inhaled solvents/gases; warfarin therapy.<br>Planned sample size: 945 women. |

**DAPIT 2004** (*Continued*)

| | |
|---|---|
| Interventions | Daily 1000 mg vitamin C and 400 IU vitamin E or placebo. |
| Outcomes | Primary outcome:<br>Incidence of pre-eclampsia.<br>Secondary outcomes: endothelial activation, birthweight centile |
| Starting date | April 2003. |
| Contact information | Dr David R McCance, Consultant Physician / Honorary Senior Lecturer, Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast BT12 6BA.<br>Email: david.mccance@royalhospitals.n-i.nhs.uk |
| Notes | |

**Fraser 2002**

| | |
|---|---|
| Trial name or title | Bi-national randomised controlled trial of vitamin C and E supplementation to prevent pre-eclampsia |
| Methods | |
| Participants | Two stratum's of participants:<br>1. nulliparous women without additional risk factors.<br>2. nulliparous women with at least one of the risk factors: diabetes, chronic hypertension, obesity, multiple pregnancy, and for multiparous women, a past history of pre-eclampsia |
| Interventions | Daily 1 g vitamin C and 400 IU vitamin E or placebo. |
| Outcomes | Frequency of pre-eclampsia, gestation hypertension with adverse conditions, intrauterine growth restriction, preterm birth |
| Starting date | Unclear. |
| Contact information | Prof W Fraser Department of Obstetrics and Gynaecology, Laval University, Quebec, Canada.<br>Email: william.fraser@ogy.ulaval.ca |
| Notes | |

**NICHD MFMU Network**

| | |
|---|---|
| Trial name or title | Combined Antioxidants and Pre-eclampsia Prediction Studies (CAPPS) |
| Methods | |
| Participants | Gestational age 9 + 0 - 16 + 6 weeks, singleton pregnancy, nulliparous,<br>BP < 135/85 mmgHg, no antihypertensive medication/diuretics, proteinuria 0 or trace, no vitamin C or E > amount in prenatal vitamins and with informed consent |

**NICHD MFMU Network** (*Continued*)

| | |
|---|---|
| Interventions | Daily dose 1000 mg vitamin C/400 IU vitamin E or placebo until delivery |
| Outcomes | Primary outcomes:<br>BP > 160/110 mmHg or BP > 140/90 mmHg > 20 weeks and one of:<br>1. SGOT (AST) > 100 U/L.<br>2. Platelets < 100,000/mm3.<br>3. Creatinine > 1.5 mg/dL.<br>4. Eclampsia.<br>5. Fetal/neonatal death.<br>6. SGA < 3rd percentile.<br>7. Preterm delivery < 32 wks. |
| Starting date | Enrolment: May 2003-April 2005.<br>Data collect on: May 2003-March 2006.<br>Closeout/final analysis: April 2006-November 2006. |
| Contact information | Prof JM Roberts, Director, Magee-Women's Research Institute<br>Professor and Vice Chair (Research) of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh.<br>Email: rsijmr@mwri.magee.edu |
| Notes | |

**Poston 2002**

| | |
|---|---|
| Trial name or title | Vitamins in Pre-eclampsia (VIP). |
| Methods | |
| Participants | Inclusion criteria:<br>1. primiparous women with no known risk factors between 14 and 21 weeks' gestation;<br>2. women at risk of pre-eclampsia (previous pre-eclampsia, essential hypertension, diabetes, SLE with renal dysfunction, APS, obesity, multiple pregnancy)<br>Exclusion criteria:<br>women unable to give informed consent or who have a daily intake of supplements vitamin C > 200 mg, vitamin E > 50 IU or those taking warfarin |
| Interventions | Daily 1 g vitamin C and 400 IU vitamin E |
| Outcomes | Incidence of pre-eclampsia, birthweight centile (< 5th). |
| Starting date | August 2003. |
| Contact information | Prof L Poston and Prof A Shennan, Maternal and Fetal Research Unit, Department of Women's Health, 10th Floor North Wing, St Thomas' Hospital, Lambeth Palace Road. London SE1 7EH.<br>Email: lucilla.poston@kcl.ac.uk or<br>andrew.shennan@kcl.ac.uk |

**Poston 2002** (*Continued*)

| Notes | |
|---|---|

AST: aspartate aminotransferase
APS: antiphospholipid syndrome
BP: blood pressure
IU: international unit
SGA: small for gestational age
SGOT: serum glutamic-oxaloacetic transaminase
SLE: systemic lupus erythematosus
U/L: units/litre
wks: weeks

## DATA AND ANALYSES

### Comparison 1. Any vitamin E supplementation

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Stillbirth | 2 | 339 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.35, 1.71] |
| 2 Neonatal death | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | 5.0 [0.64, 39.06] |
| 3 Perinatal death | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [0.67, 2.48] |
| 4 Infant death | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 5 Haemolytic anemia | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 6 Reticulocytosis | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 7 Hyperbilirubinemia | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 8 Haemoglobin levels | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 8.1 Maternal | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 8.2 Infant | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 9 Preterm birth (less than 37 weeks' gestation) | 2 | 383 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [0.78, 2.15] |
| 10 Clinical pre-eclampsia (fixed-effect model) | 3 | 510 | Risk Ratio (M-H, Fixed, 95% CI) | 0.44 [0.27, 0.71] |
| 11 Clinical pre-eclampsia (random-effects model) | 3 | 510 | Risk Ratio (M-H, Random, 95% CI) | 0.44 [0.16, 1.22] |
| 12 Intrauterine growth restriction (less than third centile or the most extreme centile reported) | 2 | 383 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.49, 1.04] |
| 12.1 Birthweight < 10th centile | 2 | 383 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.49, 1.04] |
| 13 Birthweight | 1 | 100 | Mean Difference (IV, Fixed, 95% CI) | -139.0 [-517.68, 239.68] |
| 14 Prelabour rupture of fetal membranes | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 14.1 Preterm | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 14.2 Term | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 15 Maternal death | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 16 Elective delivery and caesarean section | 1 | 55 | Risk Ratio (M-H, Fixed, 95% CI) | 1.51 [0.86, 2.63] |
| 16.1 Prelabour caesarean section | 1 | 55 | Risk Ratio (M-H, Fixed, 95% CI) | 1.51 [0.86, 2.63] |
| 17 Bleeding episodes | 2 | 339 | Risk Ratio (M-H, Fixed, 95% CI) | 0.35 [0.10, 1.23] |
| 17.1 Placental abruption | 2 | 339 | Risk Ratio (M-H, Fixed, 95% CI) | 0.35 [0.10, 1.23] |
| 18 Measures of serious maternal morbidity | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 18.1 Eclampsia | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 1.07 [0.07, 16.33] |
| 18.2 Renal failure | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 0.36 [0.02, 8.41] |
| 18.3 Disseminated intravascular coagulation | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 0.36 [0.02, 8.41] |
| 18.4 Pulmonary oedema | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 0.54 [0.05, 5.59] |
| 19 Peripheral neuropathy | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 19.1 Maternal | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

| | | | | |
|---|---|---|---|---|
| 19.2 Infant | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 20 Maternal satisfaction with care | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 21 Gestational age at birth | 1 | 100 | Mean Difference (IV, Fixed, 95% CI) | -0.40 [-1.87, 1.07] |
| 22 Congenital malformations | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 23 Apgar score less than seven at five minutes | 1 | 39 | Risk Ratio (M-H, Fixed, 95% CI) | 0.63 [0.21, 1.90] |
| 24 Vitamin K deficiency bleeding or haemorrhagic disease of the newborn | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 25 Respiratory distress syndrome | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 26 Chronic lung disease | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 27 Periventricular haemorrhage and periventricular leukomalacia | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 28 Bacterial sepsis | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 29 Necrotising enterocolitis | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 30 Retinopathy of prematurity | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 31 Bronchopulmonary dysplasia | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 32 Disability at childhood follow up | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 33 Poor childhood growth | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 34 Adverse events related to vitamin E supplementation | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 35 Side-effects of vitamin E supplementation | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 35.1 Acne | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 3.21 [0.14, 75.68] |
| 35.2 Transient weakness | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 5.36 [0.27, 106.78] |
| 35.3 Skin rash | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 3.21 [0.14, 75.68] |
| 36 Use of health service resources - maternal | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 37 Use of health service resources - infant | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 37.1 Admission to intensive care unit | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | 0.83 [0.30, 2.29] |
| 37.2 Use of mechanical ventilation | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | 0.33 [0.08, 1.46] |

**Comparison 2. Any vitamin E supplementation (sensitivity analyses by trial quality)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Stillbirth | 2 | 339 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.35, 1.71] |
| 1.1 High quality (allocation concealment = A, blinding, < 3% exclusions and use of placebo) | 2 | 339 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.35, 1.71] |
| 2 Neonatal death | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | 5.0 [0.64, 39.06] |

| | | | | |
|---|---|---|---|---|
| 2.1 High quality (allocation concealment = A, blinding, < 3% exclusions and use of placebo) | 1 | 40 | Risk Ratio (M-H, Fixed, 95% CI) | 5.0 [0.64, 39.06] |
| 3 Perinatal death | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [0.67, 2.48] |
| 3.1 High quality (allocation concealment = A, blinding, < 3% exclusions and use of placebo) | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [0.67, 2.48] |
| 4 Preterm birth (< 37 weeks' gestation) | 1 | 283 | Risk Ratio (M-H, Fixed, 95% CI) | 1.21 [0.38, 3.87] |
| 4.1 High quality (allocation concealment = A, blinding, < 3% exclusions and use of placebo) | 1 | 283 | Risk Ratio (M-H, Fixed, 95% CI) | 1.21 [0.38, 3.87] |
| 5 Clinical pre-eclampsia | 1 | 283 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.24, 0.91] |
| 5.1 High quality (allocation concealment = A, blinding, < 3% exclusions and use of placebo) | 1 | 283 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.24, 0.91] |
| 6 Intrauterine growth restriction | 1 | 283 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.50, 1.08] |
| 6.1 High quality (allocation concealment = A, blinding, < 3% exclusions and use of placebo) | 1 | 283 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.50, 1.08] |

**Comparison 3. Any vitamin E supplementation (subgroup analyses based on gestation at entry)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Stillbirth | 2 | 339 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.35, 1.71] |
| 1.1 Less than or equal to 20 week's gestation | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 1.2 Greater than 20 weeks' gestation | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.36, 1.93] |
| 1.3 Both prior to and after 20 weeks' gestation | 1 | 283 | Risk Ratio (M-H, Fixed, 95% CI) | 0.50 [0.05, 5.49] |
| 2 Preterm birth | 2 | 383 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [0.78, 2.15] |
| 2.1 Less than or equal to 20 weeks' gestation | 1 | 100 | Risk Ratio (M-H, Fixed, 95% CI) | 1.32 [0.75, 2.31] |
| 2.2 Greater than 20 weeks' gestation | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 2.3 Both prior to and after 20 weeks' gestation | 1 | 283 | Risk Ratio (M-H, Fixed, 95% CI) | 1.21 [0.38, 3.87] |
| 3 Clinical pre-eclampsia | 3 | 510 | Risk Ratio (M-H, Random, 95% CI) | 0.44 [0.16, 1.22] |
| 3.1 Less than or equal to 20 weeks' gestation | 1 | 100 | Risk Ratio (M-H, Random, 95% CI) | 0.92 [0.40, 2.13] |

| | | | | |
|---|---|---|---|---|
| 3.2 Greater than 20 weeks' gestation | 0 | 0 | Risk Ratio (M-H, Random, 95% CI) | Not estimable |
| 3.3 Both prior to and after 20 weeks' gestation | 2 | 410 | Risk Ratio (M-H, Random, 95% CI) | 0.23 [0.04, 1.46] |
| 4 Intrauterine growth restriction | 2 | 383 | Risk Ratio (M-H, Fixed, 95% CI) | 0.72 [0.49, 1.04] |
| 4.1 Less than or equal to 20 week's gestation | 1 | 100 | Risk Ratio (M-H, Fixed, 95% CI) | 0.46 [0.09, 2.41] |
| 4.2 Greater than 20 weeks' gestation | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 4.3 Both prior to and after 20 weeks' gestation | 1 | 283 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.50, 1.08] |

## WHAT'S NEW

Last assessed as up-to-date: 16 December 2004.

| Date | Event | Description |
|---|---|---|
| 7 May 2010 | Amended | Search updated. Twenty-three new reports added to Studies awaiting classification |

## HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 2, 2005

| Date | Event | Description |
|---|---|---|
| 7 July 2008 | Amended | Converted to new review format. |

## CONTRIBUTIONS OF AUTHORS

Alice Rumbold developed and wrote the protocol, extracted data and wrote the review. Caroline Crowther commented on and revised the various drafts of the protocol, extracted data and commented on all drafts of the review.

## DECLARATIONS OF INTEREST

Caroline Crowther is the chief investigator for the Australian Collaborative Trial of Supplements with vitamin C and vitamin E for the prevention of pre-eclampsia. Alice Rumbold is the PhD student involved with this trial. An independent editor will be included in the decisions regarding trial inclusion, when the trials being considered involve the two authors.

## SOURCES OF SUPPORT


### Internal sources

- Department of Obstetrics and Gynaecology, The University of Adelaide, Australia.

### External sources

- No sources of support supplied


## INDEX TERMS

### Medical Subject Headings (MeSH)

*Dietary Supplements [adverse effects]; Antioxidants [*administration & dosage; adverse effects]; Infant, Small for Gestational Age; Pre-Eclampsia [*prevention & control]; Pregnancy Complications [prevention & control]; Pregnancy Outcome; Randomized Controlled Trials as Topic; Vitamin E [*administration & dosage; adverse effects]

### MeSH check words

Female; Humans; Infant, Newborn; Pregnancy